肿瘤相关成纤维细胞在乳腺癌微环境中的研究进展

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摘　要：乳腺癌的发病率逐年上升。乳腺癌的生物学行为不仅取决于肿瘤自身，肿瘤微环境在乳腺癌的发生发展中也扮演着至关重要的角色。肿瘤相关成纤维细胞是肿瘤微环境中的重要成分，通过分泌生长因子、趋化因子等参与肿瘤的生长、侵袭与转移。

关键词：乳腺癌；肿瘤微环境；肿瘤相关成纤维细胞

Research progress of tumor-associated fibroblasts in breast cancer microenvironment

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Abstract: Breast cancer is one of the most common malignant tumors, and its incidence is increasing year by year. The biological behavior of breast cancer not only depends on the tumor itself, but also plays an important role in the occurrence and development of breast cancer. Tumor-associated fibroblasts are important components of tumor microenvironment, and participate in tumor growth, invasion and metastasis by secreting growth factors, chemokines and cytokines. This article reviews the tumor-associated fibroblasts in the breast cancer microenvironment.

Keywords: Breast cancer; Tumor microenvironment; Cancer-Associated Fibroblasts

引言：

乳腺癌是女性最常见的恶性肿瘤之一。近年来我们发现以癌症为中心的治疗方法并不足以根除恶性肿瘤，因为癌症基质也可能会促使恶性肿瘤的复发并产生治疗耐药性[1]。最近免疫治疗的进展表明，靶向肿瘤微环境也是控制肿瘤进展的强有力工具[2]。

1. CAFs的定义

肿瘤微环境即肿瘤基质，包括肿瘤细胞附近的所有非癌成分。在其的所有基质细胞中，肿瘤相关成纤维细胞（Cancer-Associated Fibroblasts，CAFs）是最丰富的，并在癌症进展中起关键作用[1]。在生理条件下，成纤维细胞以静止状态存在。当组织损伤时，它们可以被激活，并在创面愈合反应中发挥重要作用[3]。用于识别CAFs的最常见标志物是α-平滑肌肌动蛋白[4]。然而，它们的表达水平有明显的差异，其中大部分也在正常的细胞中表达[5]。

2. CAFs的来源

有报道称CAFs可能是由癌症干细胞、发生上皮-间充质转化的癌细胞、间充质干细胞或这些细胞的组合产生。目前报道最多的CAFs前体是间充质干细胞。由于脂肪组织是间充质干细胞的丰富来源，而乳腺系统嵌入在脂肪组织中，这些细胞很可能是乳腺癌中CAFs的组成部分[2]。

3. CAFs的相关介质

3.1 TGF-β

在肿瘤进展过程中，人乳腺癌CAFs越来越多地以自分泌的方式获得转化生长因子β（TGF-β）信号[6]。Weber等表示TGF-β1、外泌体等脂质介质是促进CAFs来源的细胞向CAFs转化的驱动力[7]。Kojima等通过研究表明小鼠乳腺癌细胞通过TGF-β信号启动和维持成纤维细胞向CAFs分化[8]。类似地，Neuzillet等表示肿瘤细胞可通过分泌TGF-β1逃避免疫监视[9]。Huang等研究发现在h2o2处理的成纤维细胞中，TGF-β1诱导的自噬通过上调α-SMA、FAP-α和下调Cav-1激活CAFs[10]。在Jena等的研究中提示，TGF-β1有可能通过上调p44/42 MAPK信号通路诱导耐药[11]。Zonneville等表明，CAFs通过TGF-β-纤维连接蛋白轴的机制促进肿瘤血管的形成[12]。

3.2 SDF-1

参与CAFs激活的生长因子和细胞因子如SDF-1，

对肿瘤细胞的活力也有深远的影响[2]。M.A.等人通过检测CHEK2对乳腺基质成纤维细胞的影响发现，缺乏CHEK2的间质成纤维细胞的促迁移及侵袭作用是通过增加SDF-1和IL-6的分泌来介导的[13]。Ouyang等人通过进行动物实验发现，雌激素可能通过刺激CAFs分泌SDF-1α而募集MDSCs进入肿瘤微环境发挥促肿瘤作用[14]。Papatheodorou等通过研究CXCR4和SDF1在76例浸润性乳腺癌中的免疫表达发现，SDF-1和CXCR4在癌组织中的表达均高于癌旁正常乳腺组织[15]。

3.3外泌体

外泌体是由细胞的质膜产生并释放的微小载物囊泡[16]。Chen等研究发现，CAFs释放的外泌体Wnt10b，通过典型的Wnt信号通路促进肿瘤细胞上皮间质转化导致转移[17]。Dou等表明，CAFs来源的外泌体促进乳腺癌中miR-92和PD-L1的表达，从而促进T细胞的耐受性并逃脱宿主的免疫[18]。Wu等发现，粘着斑激酶（FAK）通过整合素等细胞表面受体介导信号转导，对CAFs外泌体的调控有助于改变CAFs影响肿瘤细胞活性能力[19]。

4.结语

综上所述，CAFs在调节治疗疗效方面发挥着重要作用。然而，免疫治疗的最新进展表明，靶向肿瘤微环境是控制肿瘤进展的一个非常有力的工具。CAFs在未来改善治疗结果方面显示出巨大的潜力，靶向肿瘤微环境成为抑制乳腺癌生长和转移的一种新策略。

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